MEDICAL LIBRARY

DEC 9 1946

Volume VII DECEMBER, 1946 Number 12

DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

CONTENTS:

SOME THEORETICAL CONSIDERATIONS OF DEMENTIA PRAECOX 357
Lewis Danziger, M.D., Wauwatosa, Wisconsin

VALUE OF ELECTROENCEPHALOGRAPHY IN DIFFERENTIAL DIAGNOSIS OF EPILEPSY AND FAINTING 362
Captain Frederick C. Redlich, M.C., AUS

METABOLISM IN CEREBRAL MALARIA (Practical and Theoretical Considerations) 368
Mason Trupp, M.D., St. Louis, Missouri

BEHAVIOR AS A MEASURE OF OCCUPATIONAL FITNESS 373
Stephen Weisz, M.D., Galveston, Texas

NEUROLOGICAL CLINICAL PATHOLOGICAL CONFERENCE 376

INDEX TO VOLUME VII 381

ASSOCIATE EDITORS

A. E. Bennett, M.D. ..... Omaha, Nebraska
Francis J. Braceland, M.D. ..... Rochester, Minn.
Franklin G. Ebaugh, M.D. ..... Denver, Colorado
Temple Fay, M.D. ..... Philadelphia, Pennsylvania
Milton H. Erickson, M.D. ..... Eloise, Michigan
Hamilton Ford, M.D. ..... Galveston, Texas
Walter Freeman, M.D. ..... Washington, D. C.
George T. Harding, M.D. ..... Columbus, Ohio
Jas. K. Hall, M.D. ..... Richmond, Virginia
A. Hauser, M.D. ..... Houston, Texas
Louis J. Karnosh, M.D. ..... Cleveland, Ohio
Frank H. Luton, M.D. ..... Nashville, Tennessee
Wm. Malamud, M.D. ..... Worcester, Massachusetts
Karl A. Menninger, M.D. ..... Topeka, Kansas
Adolf Meyer, M.D. ..... Baltimore, Maryland
Glenn Myers, M.D. ..... Los Angeles, California
Hans H. Reese, M.D. ..... Madison, Wisconsin
Theodore A. Watters, M.D. ..... New Orleans, La.
S. Bernard Wortis, M.D. ..... New York, N. Y.

Titus H. Harris, M.D.
Galveston, Texas
Editor-in-Chief

George Biegeir, B.S., LL.B.
Chicago, Illinois
Managing Editor

THE
RING SANATORIUM AND HOSPITAL
Arlington Massachusetts

Eight miles from Boston at an elevation of 400 feet

Specializing in the individualized care of Neuropsychiatric illnesses and Habit conditions. All accepted Therapies under the direction of a resident medical staff and trained assistants. Cottage plan permits a variety of accomodations.

67th Year

VOLTA ROSS HALL, M.D.
Medical Director

HALLAM T. RING
Administrator

In conjunction: The Ring School of Attendant Nursing

THE HARDING SANITARIUM
WORTHINGTON, OHIO

For Nervous and Mental Disorders

NINE MILES NORTH OF STATE HOUSE—COLUMBUS

GEORGE T. HARDING, M.D., *Medical Director*

HARRISON S. EVANS, M.D.
CHARLES L. ANDERSON, M.D.
HAROLD CAVINESS, M.D.
HENRY E. ANDREN, M.D.

Telephone: Columbus FR. 2-5367

COMPTON SANITARIUM
AND
LAS CAMPANAS HOSPITAL
COMPTON, CALIFORNIA
(Near Los Angeles)

Compton Sanitarium is a private psychiatric hospital with 120 beds. Emphasis is given psychotherapy by a staff of resident phychiatrists. Other treatment procedures are duly evaluated and administered. Careful records are maintained. There are psychiatrically trained graduate nurses; student nurses through affiliation; nursing attendants; dietitian; ocupational therapist; recreational therapist; hydrotherapist; masseuse. Las Campanas Hospital (43 beds) provides adjunct general hospital facilities. Compton Sanitarium and Las Campanas Hospital are approved by the American College of Surgeons.

GLENN MYERS, M.D.
Medical Director.

Beverly Hills Sanitarium
for
The Study and Treatment of Nervous and Mental Diseases

218 No. Westmoreland DALLAS 11, TEXAS Telephone W-3114

This sanitarium is a psychopathic hospital with a home-like environment and is equipped to treat psychiatric and neurological cases in a most scientific manner by means of psychotherapy, occupational therapy, recreational therapy and physiotherapy, including insulin and electro-shock treatments; electroencephalograph available.

ARTHUR J. SCHWENKENBERG, M.D.
Neuropsychiatrist
STEPHEN WEISZ, M.D.
Assoc. Neuropsychiatrist and Clinical Director

Staff Physicians
JANE N. CREEL, M.D.
E. C. WINKELMANN, M.D.

VOL. VII DECEMBER, 1946 No. 12

EDITORIAL OFFICES
UNIVERSITY OF TEXAS SCHOOL OF MEDICINE
800 AVENUE B., GALVESTON, TEXAS

BUSINESS OFFICES
PHYSICIANS POSTGRADUATE PRESS
500 NORTH DEARBORN ST., CHICAGO 10, ILLINOIS

COPYRIGHT, 1946 BY
PHYSICIANS POSTGRADUATE PRESS

DISEASES of the NERVOUS SYSTEM

(PUBLISHED MONTHLY)

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Some Theoretical Considerations of Dementia Praecox

LEWIS DANZIGER, M.D.*
Wauwatosa, Wisconsin

In earlier studies (Danziger,[1] Danziger and Kindwall[2]) experimental data were presented showing the probability of recovery from dementia praecox under two different conditions, namely: when shock therapy is given and when the treatment is only symptomatic. It remains to construct a theory which will predict these experimental results and which will suggest new studies of the disorder. Such a theory is proposed in this paper. It is believed to be simpler than one suggested in an earlier report (Danziger and Landahl[3]).

I. *Symptomatic Treatment.* Let us assume that dementia praecox is caused by some unknown material, call it u, which is produced in the body at a constant rate and which is excreted or otherwise disposed of at a rate proportional to the amount of u present. That is, homeostatic mechanisms will operate to clear the body of u, and the more u is present, the more will be removed. The rate of increase of u will then be

$$\frac{du}{dt} = a - bu \qquad (1)$$

where a is the rate at which u is produced and b is the homeostatic constant. (If the disorder is caused by a deficiency rather than a toxin, and homeostatic mechanisms act to conserve the critical material, the left hand member of *(1)* becomes negative. Except for this change in sign, the argument is not altered).

*Milwaukee Sanitarium and Clinical Instructor in Psychiatry, Marquette University.

Integrating *(1)* and remembering that when $t = 0$, $u = 0$, we have

$$u = \frac{a}{b}(1 - e^{-bt}) \qquad (2)$$

Thus, u increases rapidly early in the disease, when t is small; but the rate of increase eventually becomes very small and a new equilibrium is reached in the region of $u = \frac{a}{b}$.

The probability of eventual recovery may be assumed to decline as u increases. Let us assume that the probability declines in accordance with a simple decay law, for example:

$$P = P_o e^{-ku} \qquad (3)$$

which may more conveniently be written:

$$\log P = \log P_o - ku \qquad (3a)$$

where P is the probability of eventual recovery, P_o is the probability at some arbitrary u, say $u = 0$, and k is a constant. If u is expressed in units of mass, k must have the dimension mass^{-1} since P and P_o are without dimensions. Since nothing is known as yet as to the nature of u or the mass of u present, the value of unity is arbitrarily assigned to k, in relation *(3a)*.

From U. S. Bureau of the Census data,[1] it is seen that on the day of admission to the hospital, the probability of eventual recovery is *0.0545*. From this observation and *(3)*, it is possible to calculate the probabilities for all later periods of hospitalization and to extrapolate back to the time when recovery

was certain, namely about the time when $u = 0$. The agreement between *(3)* and observation is shown in Figure 1. The increase in u with time is shown in Figure 2.

Strictly speaking, recovery is impossible if a is greater than b and if a and b are really constants. Actually, a and b may vary through fairly wide limits in the individual patient, while their mean values for a large group will remain quite stable. Relation *(2)* gives the mean value of u for a large group of patients ill for some definite time t. Although each of the patients in the group has been sick for t units of time, some may be growing worse while others are improving and others are stationary. If we know nothing of the patients except that they have been ill for t units of time, what is the probability that any one of them, selected at random, will ever recover? The answer is given by relation *(3)* and obviously is neither affirmative nor negative, but a probability. It is just such a probability that is demanded of the clinician and it is just such a probability that the clinician unconsciously calculates when he gives the prognosis for an individual patient, although he may be aided by having at his disposal more information than simply the duration of the illness.

Extrapolation of *(3)* to $u = 0$, gives to t a value of about -22 months. That is, the disease begins on the average about 22 months before hospitalization. This value, $t_o = -22$, is somewhat larger than clinical judgment would suggest is correct. Possible explanations for this error are:

1. the disease may be present for some time before clinical symptoms are recognized,

2. hospitalization may be of benefit; that is, after hospitalization, the value of b is increased,

3. both 1 and 2. This third possibility is in accord with clinical and popular judgment. Hill[4] in a survey of over half the patients admitted to state psychiatric hospitals in the United States in 1910, found that 64.5 per cent were admitted in the first year of the illness and that 54 per cent were admitted in the first half year of the illness. His figures are for all types of disorders taken together.

II. *Shock Treatment.* The probability of recovery under symptomatic treatment may be compared now with the probability of recovery under shock therapy.

Let us assume that some portion, r, of u is removable by treatment and that each treatment removes some fraction, nr, of u, but that each treatment has a constant toxic effect, m. Let us assume also that the effect of each treatment persists for a few days until the next treatment can be given, and

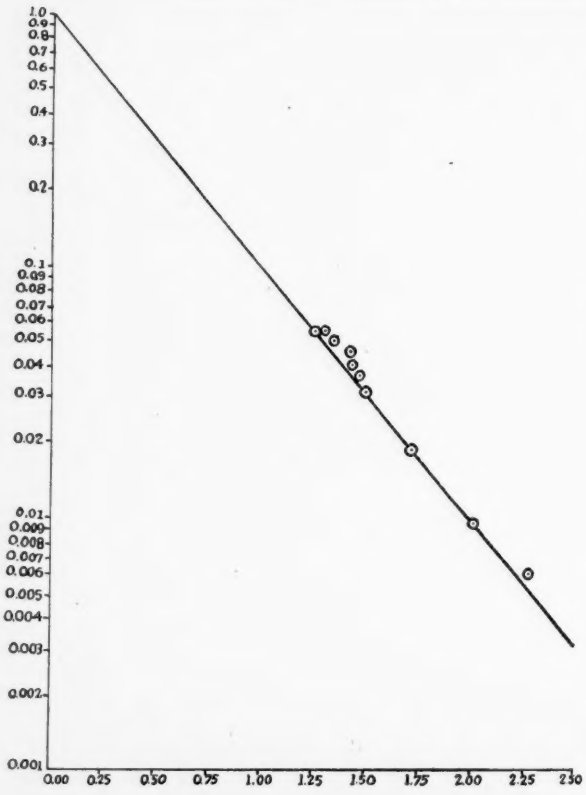

Figure 1: Probability of recovery from dementia praecox treated in state hospitals in 1933. Agreement between theory (equation 3) and observation (Danziger[1]). Ordinate, probability of eventual recovery in the hospital. Abscissa, the quantity u which increases with time in accordance with equation 2 and Figure 2.

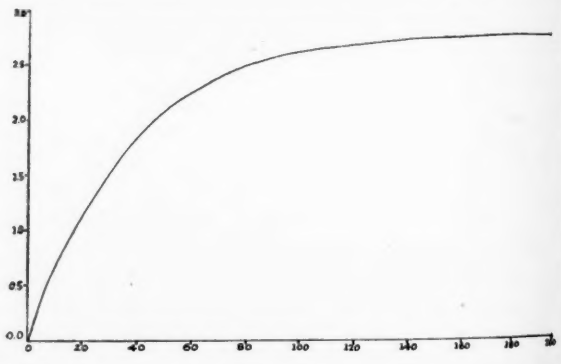

Figure 2: Increase of the postulated material, u, with time, as given by equation 2. Ordinate, u in arbitrary units of mass. Abscissa, duration of illness in months. Constants are:
$a = 0.077$; $b = 0.027$.

that the treatment effect may be considered (at least as a first approximation) as a linear function of the treatment time. Then the rate at which r is removed is

$$\frac{dr}{dT} = m - nr \qquad (4)$$

where T is the time during which treatments are given. Since r is presumably large when treatment is started, the right hand member of *(4)* will be negative. Integrating *(4)*, we obtain the amount of r removed by treatment

$$r = \frac{m}{n}(1 - e^{-nT}) \qquad (5)$$

Then

$$u = u_o - r \qquad (6)$$

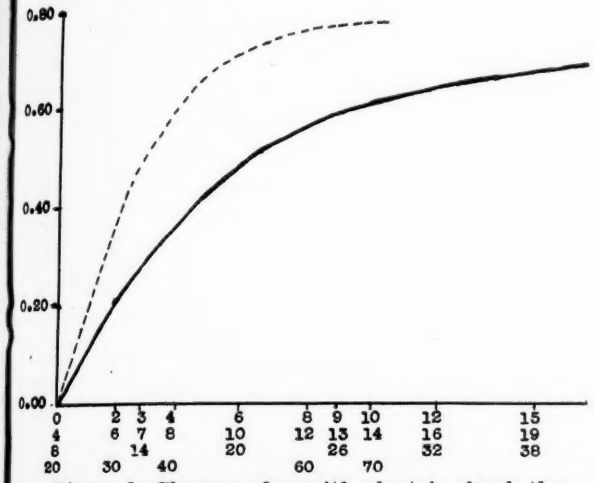

Figure 3: Change of w with electric shock therapy represented by solid line. Change of w with insulin shock therapy represented by dotted line.
Scale (a): Effective treatment time in weeks.
Scale (b): Treatment time in weeks.
Scale (c): Number of electric shock treatments (given in most cases at the rate of two per week).
Scale (d): Number of comas (given in most cases at the rate of five per week).

Note that the curves pass through the T axis at $T = 4$, which is interpreted to mean that 8 treatments were without effect, either because only petit mal seizures were produced with electric shock or because some treatments were given after the patient had recovered. The number of treatments exceeds the number of effective treatments by 8.

Equation is: $w = \frac{0.147}{0.210}(1 - e^{-0.21T^*})$

In the cases of insulin shock the coincidence that the curve passes through the T axis at $T = 4$ is interpreted to mean that 20 comas were without effect either because they were too short or shallow or because they were experienced after the patient had recovered. The number of comas exceeds the number of effective comas by 20. Effective treatment time, $T^* = T - 4$.

Equation is: $w = \frac{0.32}{0.40}(1 - e^{-0.4T^*})$.

That is, the u left in the patient will be the amount present when treatment was started minus the amount removed by treatment. Actually u_o is increasing in accordance with *(2)* during the time of treatment, but it may be considered constant as a first approximation. Define

$$w = \frac{r}{u_o}$$

as the fraction of u_o removed by the whole course of treatment. Substituting in *(6)* we obtain

$$u = u_o - u_o w = u_o(1 - w) \qquad (7)$$

Substituting *(7)* in *(3)*, we obtain a new expression giving the prognosis under symptomatic or shock treatment. When no shock treatment is given, $w = 0$.

The value of w may be determined only indirectly at present. From the available data,[2] w is given approximately by the curves in Figure 3. In Figure 4 is shown the agreement between previously reported experimental results and the relation

$$\log P = \log P_o - k u_o (1 - w) \qquad (8)$$

The difference between observed and calculated probabilities of recovery is less than 0.06 for about one half the points and less than 0.10 for about two thirds of the points.

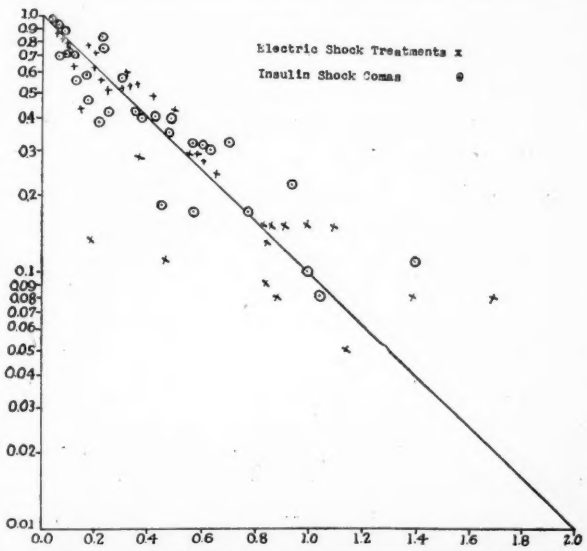

Figure 4: Probability of recovery from dementia praecox if adequate electric shock therapy is given indicated by crosses (x). Probability of recovery from dementia praecox if adequate insulin shock therapy is given indicated by circles (o).

Agreement between theory (equation 8) and observation (Danziger & Kindwall[2]). Ordinate, probability of immediate recovery. Abscissa, the quantity $u = u_o(1 - w)$.

Such agreement is fairly good, considering the small number of observations and the difficulty of determining the duration of illness.

It will be noted that the value of w reaches zero at $T = 4$ *weeks* for both insulin and electric shock therapy. This is interpreted as meaning that some treatments were without effect because of technique (only petit mal seizures or short, shallow comas) or because they were given after the patient had recovered. Both reasons are plausible. It was the policy in most cases to give more treatments after recovery in order to stabilize the improvement.

III. *Interpretation.* A possible interpretation of the meaning of u may be of some interest. If u is interpreted as grams of a toxic substance, it might be thought of as interfering in some way with the normal metabolism of the brain and perhaps of other organs. More specifically, it might be considered an inhibitor of respiration, perhaps by inhibition of one or more of the respiratory enzymes. That such a pathogenesis of abnormal behavior is possible has already been suggested (Danziger[5]). Further evidence in support of this interpretation will now be presented.

Malzberg[6] has prepared life tables showing the age and sex specific death rates for patients of the New York state civil psychiatric hospitals and for the normal population of New York. It turns out that the death rates for the patients are much higher than for the remainder of the population. Malzberg's figures are for 1920 and hence are not influenced by the results of shock therapy. It is apparent that supplying the patients with adequate housing, food, clothing, nursing and medical attention as defined by New York state civil psychiatric hospital standards in 1920 was not sufficient to compensate for the force of mortality exerted by the mental disorders. Malzberg's findings may be summarized for ages 20 to 60 by the empirical relation

$$\log R_a = f - g(H_a - y) \qquad (9)$$

where R_a is the age and sex specific death rate, as given by Malzberg

f and g are constants

H_a is the rate of heat production per unit of body surface area for the given age and sex, as shown in the tables of Boothby and Sandiford[7]

y is a function of the value of u at the time of death.

The correspondence between Malzberg's data and equation *(9)* is shown in Figure 5. Close agreement is not to be expected because the death rates of the patients are not shown according to psychosis, while the mean value of u at death might be expected to vary in the several types of illness. For the patient population, y has a value of 4.5 for men and 3.5 for women, which is 9.6 to 12.6 per cent of H_a depending on the age at death. For the remainder of the population, $y = 0$. By assuming, then, that the rate of heat production is reduced by 9.6 to 12.6 per cent (that is, by an amount barely detectable by present methods) the high death rates of the psychotic patients are explained, at least formally.

Hoskins[8] in a careful study of the basal metabolic rates in patients with dementia praecox, found a mean depression of about 12 per cent. Gjessing[9] described changes in the oxygen consumption and nitrogen balance in a group of patients who fluctuated rapidly between states of comparatively good health and catatonic excitement or stupor. His findings indicate also that the proposed value of

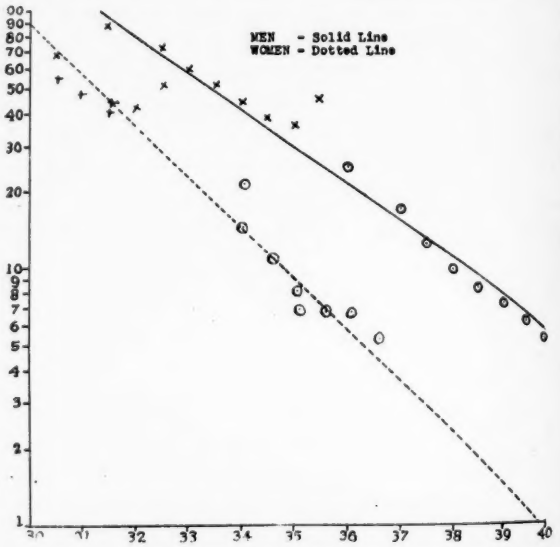

Figure 5: Agreement between equation 9 and data for men aged 20 to 60 and for women aged 20 to 60 (Malzberg[6]). Ordinate, age specific death rate per 1,000 population. Abscissa, the quantity $H_a - y$, in calories per square meter per hour. Patient population death rates indicated by (x), normal population death rates by (o). For normal population, $y = 0$; for male patients, $y = 4.5$; for female patients, $y = 3.5$.

y is of the correct order of magnitude. His oxygen consumption curves indicate changes in the metabolic rate correlated (sometimes after a latent period) with changes in the clinical state. This is consistent with the idea of a shifting pace maker in the respiratory enzyme system, as suggested by Hoagland.[10]

From the Arrenhius equation, Hoagland predicted that the logarithm of the mean alpha frequency of the electroencephalogram would be a linear function of the reciprocal of the absolute temperature of the patient. He was able to confirm this in paresis, and suggested that the slope of the curve is a measure of the activation energy of the pace making enzyme. He then found that the slope changes in paresis as the disease progresses, and suggested a biochemical lesion in the iron containing oxidases. Such a lesion is consistent with the presence of free iron in the brains of paretics.

By similar reasoning, it is easy to propose the following experiment: Electroencephalograms should be taken in a sufficient number of cases of dementia praecox at body temperatures varying over a few degrees centigrade. The mean alpha frequencies should be determined and their logarithms plotted against the reciprocal of the absolute temperature of the patient. The plotted points should fall on a straight line, the slope of which is readily determined. The experiment should then be repeated on the same patients after their recovery and perhaps during the course of shock therapy. If the theory is correct, the slopes should change and should approach normal as the patients improve. If such changes occur, it should be possible to give a tentative localization of the postulated biochemical lesion.

Summary

The theory here proposed may be summed up as follows: An unknown toxic substance accumulates in the body of the patient at a rate which is specified. The substance is assumed to depress the rate of heat production, perhaps by inhibiting one of the respiratory enzymes and forcing the enzyme system to act under an abnormal pace maker. Shock therapy is assumed to remove the postulated toxic material at a rate which is specified. The theory leads to equations which describe the results of symptomatic and shock therapy in dementia praecox, and also gives an explanation of the high death rates observed in patients with mental disorders.

References

1 Danziger, L.: "Prognosis in Some Mental Disorders," *Dis. of Nerv. Syst.*, 7: 229, 1946.

2 Danziger, L., and Kindwall, J. A.: "Prediction of the Immediate Outcome of Shock Therapy in Dementia Praecox," *Dis. of Nerv. Syst.*, 7: 299, 1946.

3 Danziger, L., and Landahl, H. D.: "Some Quantitative Aspects of Shock Therapy in Psychoses," *Bull. Math. Biophysics.*, 7: 213, 1945.

4 Hill, J. A.: "Insane and Feeble Minded in Institutions," *U. S. Govt. Print. Off.*, Washington, D. C., 1914.

5 Danziger, L.: "Anoxia and Compounds Causing Mental Disorders in Man," *Dis. of Nerv. Syst.*, 6: 365, 1945.

6 Malzberg, B.: "Social and Biological Aspects of Mental Disease," *State Hospital Press*, Utica, N. Y., 1940.

7 Boothby, W. M., and Sandiford, I.: "Normal Values of Basal or Standard Metabolism," *Proc. 13th Internat. Physiol. Cong.*, 1929.

8 Hoskins, R. G.: "Oxygen Consumption ('Basal Metabolic Rate') in Schizophrenia; Distribution in 214 Cases," *Arch. Neurol. and Psychiat.*, 28: 1346, 1932.

9 Gjessing, R.: "Disturbances of Somatic Functions in Catatonia with Periodic Course and Their Compensation," *J. Ment. Sc.*, 84: 608, 1938.

10 Hoagland, H.: In J. Alexander's "Colloid Chemistry," *Reinhold Pub. Co.*, New York, 1944.

Value of Electroencephalography in Differential Diagnosis of Epilepsy and Fainting

CAPTAIN FREDERICK C. REDLICH, M.C., AUS

Prior to and during the first years of World War II the diagnosis of epilepsy in an Army patient could be made only after an epileptic seizure had been observed by a medical officer. After the Army began to use electroencephalography for the diagnosis of neurological and psychiatric diseases, an abnormal electroencephalogram (EEG) was accepted as a satisfactory criterion for the diagnosis of convulsive disorder. The first change in the regulations regarding the diagnosis of epilepsy was reported by Roseman[1] in his paper on clinical and electroencephalographic observations on 364 epileptic patients at Walter Reed General Hospital.

A Technical Bulletin (TB Med. 76) describing EEG technique, classification and some basic rules of interpretation was issued by the Surgeon General's office attempting to set a uniform working method for electroencephalographers in Army installations. The classification was based on the work of F. A. Gibbs, E. L. Gibbs, and W. G. Lennox,[2] who studied 730 epileptics and 1000 normal control subjects. According to this classification, EEG records were divided into comparatively simple patterns. Interpretations were based on statistical distributions. However, no definite criteria in regard to interpretations were given to military electroencephalographers, nor are such criteria reported in the literature. It was obvious that in some instances the EEG just confirmed a diagnosis. In other instances when the clinical diagnosis was uncertain or obscure, it helped to determine a diagnosis.

The present investigation attempts to examine the usefulness of clinical electroencephalography in 1) a group of patients with clinically well established diagnosis of epilepsy, fainting and hysterical fits and 2) a group of patients in whom the differential diagnosis of convulsive seizures, various types of syncope and of hysterical fits could not be established. In other words, the following questions in regard to patients with fits and faints were examined:

1. What is the value of clinical electroencephalography as a confirmatory test?
2. What is the value of clinical electroencephalography as a determining test?
3. What is the relation of the interpretation of electroencephalography to clinical judgment?

Method

The standard technique as outlined in TB Med. 76 was followed. The electrical activity of the frontal, motor, temporal and occipital areas was recorded by monopolar leads with the patient at rest, and during and after three minutes of over-ventilation. When EEG's in patients were found to be normal during the first run, the test was usually repeated.

The following categories of the classification of Gibbs, Gibbs and Lennox[2] were used:

1. *Paroxysmal records:* a. Petit mal variant (PMV), b. Petit mal (PM), c. Psychomotor (Psy), d. Spikes (Sp), e. Grand mal (GM).
2. *Slow records:* a. Very slow (S_2), b. Slow (S_1).
3. *Fast records:* a. Very fast (F_2), b. Fast (F_1).
4. *Normal records.* With the exception of the occurrence of petit mal (PM) waves during over-ventilation only the character of waves before and after 1½ minutes over-ventilation was considered significant for such a classification.

Observations

The 215 subjects, patients in an Army Neurological Center, were divided into two groups:

1. 134 patients with clinically well established diagnosis of (a) epilepsy (paroxysmal disorder, cause unknown), (b) fainting, (c) hysterical fits.
2. 61 patients with loss of consciousness in whom the differential diagnosis between epilepsy and fainting could not be established on clinical grounds.

The distribution of EEG findings in the

first subgroup is presented in Table I. The majority of these patients belonged to the grand mal group. In only 11 of the 95 patients could seizures be observed by medical officers. In the other patients the diagnosis was satisfactorily established—not from an Army point of view—but on the ground of the following clinical evidence. A reliable history was obtained of tonic clonic seizures with loss of consciousness in 89 patients (Grand Mal), of short bouts of bizarre psychomotor behavior with amnesia in 5 patients (Psychomotor epilepsy), and of frequent short staring spells, chewing movements and amnesia (Petit mal epilepsy) in 1 patient. Many patients gave a history of aura. They were completely unconscious and had amnesia for the period of unconsciousness and a short period of time thereafter. They occasionally hurt themselves falling or gave histories of tongue biting and of urinary incontinence. Many experienced seizures while they were asleep. A few patients gave a positive family history of elipepsy.

Neurological and psychiatric examinations were non-contributory. None of the patients showed any deterioration or gross personality changes. Routine blood, urine and spinal fluid findings were negative. Carbohydrate tolerance test, non-protein nitrogen and carotid sinus pressure tests were negative. All patients having seizures only at rare intervals were considered as mild epileptics.

EEG findings of the subgroup of 29 patients with fainting are presented in Table II. In these patients fainting without convulsions and without muscular contractions was observed in 7 and a reliable history was obtained in the others. Orthostatic syncope, sensitivity of the carotid sinus and hypoglycemic coma were ruled out by clinical examinations and laboratory tests. An attempt was made to differentiate this group by a division into hysterical and vasodepressor fainting as outlined by Romano and Engel.[3] In 14 patients no such differentiation could be made because their fainting attacks resembled sometimes the one and sometimes the other form.

The third subgroup consisted of 10 patients with hysterical fits. In four of these, fits were observed by medical officers. The fits consisted in dramatic generalized seizures without any tonic clonic phase. They were preceded by tension and anxiety. In these patients no complete loss of consciousness was noted; they remained partially aware of their environment and responded to strong sensory stimuli; no tongue biting, or incontinence occurred. These patients were emotionally labile, suggestible, immature individuals with a tendency toward other conversion symptoms; their fits were provoked by anxiety and tension raising circumstances. In 3 patients such seizures were induced by suggestion during an electroencephalographic examination

TABLE I

PATIENTS WITH EPILEPSY *(Clinical Diagnosis Established)*

	BRAIN WAVES										
Clinical Diagnosis	*PMV*	*PM*	*Psy*	*S_2*	*S_1*	*N*	*F_1*	*F_2*	*Sp*	*GM*	*Total*
Grand Mal	1	4	7	23	8	16	13	11	2	4	89
Psychomotor	0	1	2	1	1	0	0	0	0	0	5
Petit Mal	0	0	0	1	0	0	0	0	0	0	1
TOTAL	1	5	9	25	9	16	12	11	2	4	95

TABLE II

PATIENTS WITH FAINTING *(Clinical Diagnosis Established)*

	BRAIN WAVES										
Clinical Diagnosis	*PMV*	*PM*	*Psy*	*S_2*	*S_1*	*N*	*F_1*	*F_2*	*Sp*	*GM*	*Total*
Vasodepressor Fainting	0	0	0	1	1	4	1	0	0	0	7
Hysterical Fainting	0	0	0	0	0	5	3	0	0	0	8
Fainting (undifferentiated)	0	0	1	0	2	8	2	1	0	0	14
TOTAL	0	0	1	1	3	17	6	1	0	0	29

and no EEG changes were noted. Eight of these 10 patients had a normal EEG, one had a very slow (S_2) record and one had a fast (F_1) record.

The second main group consisted of 61 patients in whom the author, assisted by other neurologists of the service, was unable to make a definite clinical diagnosis. Patients and their EEG findings are presented in Table III. The patients in this group had rather heterogenous syndromes. In an attempt to differentiate these 61 patients on clinical grounds, the following subdivisions were made: (a) Patients with mostly complete loss of consciousness who "stiffened out" during their period of unconsciousness, although no real convulsive movements were reported. (b) Short lapse of memory, depersonalization or total amnesia, without the ordinary criteria for petit mal or psychomotor attacks. Narcotherapy failed to clear up the amnesia. (c) Presence of myoclonic twitching with occasional fainting but without grand mal convulsions and with normal neurological findings. (d) Patients who most probably exhibited grand mal convulsions at certain times, but whose fits were hysterical in nature at other times. The personalities of these patients were characterized by immaturity, emotional lability, suggestibility and a tendency to develop conversion symptoms under stress. This group manifested what has been called "hysteroepilepsy" by some of the earlier authors. (e) Bizarre aggressive or sexual (exhibitionistic) behavior in immature, suggestible patients; by means of narcotherapy it was possible to clear up the accompanying amnesia to some extent. (f) Prolonged fugue states with amnesia in hysterical and asocial personalities. (g) Short staring spells which could neither be classified as petit mal nor as oculogyric crises.

Discussion

The data of Gibbs, Gibbs and Lennox have interpretive value on a statistical basis. Thus, according to these investigators paroxysmal records which were 33 times as frequent in epileptics as in normals were called extremely abnormal or strongly suggestive of epilepsy; very fast (F_2) and very slow (S_2) records, 30 times as frequent in epileptics as in normals, were called very abnormal and suggestive of epilepsy; fast (F_1) and slow (S_1) records, only twice as frequent in epileptics as in normals, were called mildly abnormal or consistent with the diagnosis of epilepsy, but not definitely suggestive of such a disorder. The present author based his interpretations on the statistical distributions of Gibbs, Gibbs and Lennox as well as on the specific circumstances of the Army patient.

The electroencephalogram is not a laboratory test which proves or disproves epilepsy with absolute or even a high degree of certainty. It rather supports or contradicts clinical evidence to a greater or lesser degree; in known conditions it will tend to be a con-

TABLE III

DISORDERS ALLIED TO EPILEPSY AND FAINTING WITH UNCERTAIN CLINICAL DIAGNOSIS

	BRAINWAVES										
Clinical Diagnosis	*PMV*	*PM*	*Psy*	*S_2*	*S_1*	*N*	*F_1*	*F_2*	*Sp*	*GM*	*Total*
Fainting with Muscular Rigidity	0	1	1	1	7	18	7	0	1	1	37
Amnesia (Unclear Etiology)	0	0	0	0	0	3	1	0	0	0	4
Myoclonic Twitching with Fainting	0	0	1	0	1	0	0	0	0	0	2
Hysterical Patients with Epileptic Fits	0	0	1	1	2	2	1	1	0	0	8
Bizarre Psychomotor Behavior	0	0	1	1	3	0	0	0	0	0	5
Fugue States	0	0	0	0	0	0	1	1	0	0	2
Staring Spells	0	0	0	0	0	3	0	0	0	0	3
TOTAL	0	1	4	3	13	26	10	2	1	1	61

firmatory test according to what statisticians and epistemologists call a probability calculus; similarly in a choice between two conditions it will tend to tip the scale in favor of one or the other.

With consideration as to the purpose of the diagnosis in mind the following point of view was adopted:

I. a. In patients with clinically certain diagnosis of epilepsy: paroxysmal, very fast (F_2) and very slow (S_2) records were considered confirmatory of the diagnosis. b. In patient with the diagnosis of epilepsy fast (F_1) and slow (S_1) records were considered indeterminate as to their diagnostic contribution. From a practical point of view fast (F_1) and slow (S_1) EEG's were usually counted as consistent with solidly established clinical diagnoses of epilepsy. Particularly from the angle of military dispositions such interpretations were convenient and justified. In the last analysis it was felt that clinical judgment of a high degree of probability should not be overruled by EEG findings. A persistently normal EEG in epileptic patients was considered as not confirmatory.

II. In patients with a proven diagnosis of fainting and of hysterical fits normal records were considered as confirmatory; fast (F_1) and slow (S_1) records as indeterminate; paroxysmal, very fast (F_2) and very slow (S_2) records as non-confirmatory.

III. In the group of patients with an unsettled differential diagnosis of epilepsy and fainting paroxysmal, very fast (F_2) and very slow (S_2) records were considered as determinate for epilepsy; normal EEG as determinate for fainting. Fast (F_1) and slow (S_1) records were interpreted as indeterminate.

Based on the forementioned procedure the value of the EEG in patients with firmly established diagnoses is presented in Table V. It must be stressed that from the viewpoint of military neurology a confirmation of the clinical diagnoses in 61.2 per cent is a very valuable contribution. Actually this number is somewhat smaller as epileptic seizures and hysterical fits were observed by competent witnesses and thus according to Army regulations diagnoses were made without the aid of the EEG. In civilian practice, of course, such a confirmatory test is of much less aid.

The more important contribution of the EEG in military and civilian neurological practice is its determinate role in uncertain conditions. In this our patient material strictly using the outlined criteria the EEG was of definite diagnostic aid in almost two thirds of the cases (Table VI). This degree of diagnostic contribution was surprising to the author who originally considered clinical electroencephalography as primarily a confirmatory method. The data would indicate that clinical electroencephalography, with a statistical approach, is more useful than would

TABLE V

VALUE OF EEG IN PATIENTS WITH CONDITIONS ALLIED TO EPILEPSY AND FAINTING WITH UNCERTAIN CLINICAL DIAGNOSIS

Value of EEG	*Number of Patients*
Diagnosis of Epilepsy Determined by EEG	12 (19.6%)
Diagnosis of Fainting Determined by EEG	26 (42.7%)
All Diagnoses Determined by EEG	38 (62.3%)
No Diagnoses Determined by EEG	23 (37.7%)

TABLE IV

VALUE OF EGG IN PATIENTS WITH ESTABLISHED CLINICAL DIAGNOSIS

	VALUE OF EEG			
Clinical Diagnosis	*Confirmatory*	*Indeterminate*	*Non Confirmatory*	*Total*
Epilepsy	57 (60%)	22 (23.2%)	16 (16.8%)	95 (100%)
Fainting	17 (58%)	9 (31.6%)	3 (10.4%)	29 (100%)
Hysterical Fits	8 (80%)	1 (10%)	1 (10%)	10 (100%)
TOTAL	82 (61.2%)	32 (23.9%)	20 (14.9%)	134 (100%)

appear from the review of the subject by Finley and Dynes.[4]

Particular instances in which the EEG permitted the surprise diagnosis of psychomotor epilepsy of course are rare in military neurology because such patients are so infrequent in the Armed Forces. However, the method was of considerable interest and usefulness in the differential diagnosis of obscure conditions as outlined in Tables III and V. It was of particular help in the differentiation of various amnesia states as Lennox[5] pointed out in his paper on true and feigned amnesias. EEG helped to disentangle the complex diagnostic problems of hysterical personalities with epileptic seizures. It helped in the differentiation of the vague group of "fainting with muscular rigidity" when no definite diagnosis of epilepsy could be made.

These data are in general agreement with other authors, Roseman,[1] Harty, Gibbs and Gibbs,[6] Robinson,[7] Schwab,[8] Solomon, Harrison, Wittson and Hunt,[9] and Silverman,[10] who reported on electroencephalography of epileptic patients in the armed forces. In particular, it bears out Roseman's observation that the petit mal and psychomotor types in the Armed Forces are comparatively rare and that grand mal seizures can very seldom be observed by qualified observors. In service the main problem remains the differentiation of mild types of grand mal epilepsy from various forms of fainting and hysterical fits. In this respect clinical electroencephalography makes a very definite contribution.

EEG findings during various types of fainting have been described by Engel and Margolin,[11] Engel, Romano and McLin,[12] Gibbs and Forster,[13] Forster, Roseman and Gibbs,[14] Romano and Engel,[3] Romano, Stead and Taylor.[15] The only study examining the EEG of fainting patients outside of their attacks was recently published by Levin, Katz and Greenblatt.[16] The figures of these authors show a trend similar to the results published in this paper. In the patients of Levin and associates only 4 per cent EEG abnormalities in 114 patients were noted in the 114 patients with simple fainting while 45 per cent of 11 patients exhibiting muscular rigidity during their syncope showed abnormal EEG's. The electroencephalographic method thus definitely helps to break down the vague entity of "fainting".

The author found the classification outlined by Gibbs, Gibbs and Lennox to be valuable. It is simple, statistically significant and clinically valid. The only change which suggested itself to the author was the addition of a group of mixed fast and slow (F_1S_1) abnormalities. This group characterized by a combination of slow and fast waves of various degrees with a choppy dysrythmic appearance seemed to be more suggestive of epilepsy than the mere fast (F_1) or slow (S_1) groups. In order to conform to the already existing large body of data, however, this dysrythmic group was broken down into fast (F_1) and slow (S_1) groups as Gibbs, Gibbs and Lennox suggested.

Though the classification of Gibbs, Gibbs and Lennox was used the diagnostic features as outlined by Jasper and Kershman[17] and later by Echlin[18] were noted. At present it seems that the criteria of these authors offer little clinical help in patients with generalized seizures but the author agrees with Finley and Dynes[4] that emphasis on localizing features may lead to a better future understanding of the physiology of paroxysmal disorders.

The small group of patients with paroxysmal disorders who had normal electroencephalograms and of fainters with abnormal EEG's deserve particular attention from clinicians and electroencephalographers. One attempt to differentiate the epileptic group with normal EEG's diagnostically from patients with syncope was made by Blier and Redlich.[19] These authors examined the EEG's of epileptic patients and fainters before and after the pitressin hydration test and noted a much greater tendency toward cerebral dysrythmia in the epileptic group.

Summary

The value of clinical electroencephalography as a confirmatory and determinate diagnostic method was examined in 215 patients of an Army Neurology Center. Ninety-five patients had a clinically certain diagnosis of epilepsy; 29 patients had a clinically certain diagnosis of fainting, 10 of hysterical fits; and in 61 patients the differential diagnosis of epilepsy and fainting could not be made on clinical grounds.

A standard procedure and a classification

outlined by Gibbs, Gibbs and Lennox was adopted. The type and distribution of EEG tracings in these patients is presented in the text. Interpretations are based on statistics in the material of Gibbs, Gibbs and Lennox and on considerations implied by the clinical and military situation.

In the group of proven epileptics the EEG was confirmatory in 57 (60%), indeterminate but consistent in 22 (23.2%) and not confirmatory in 16 (16.8%). It was confirmatory in 17 (58%) of the proven fainters; indeterminate and consistent in 9 (31%) and not confirmatory in 3 (10.4%); in 8 patients with hysterical fits it was confirmatory, in 1 indeterminate and in 1 not confirmatory. In all patients with a clinically certain diagnosis the EEG then was confirmatory in 82 (61.2%), indeterminate in 32 (23.9%) and not confirmatory in 20 (14.9%).

In 61 patients with an unsettled differential diagnosis of fainting and/or epilepsy, the EEG test helped to determine the diagnosis of epilepsy in 12 (19.6%) and of fainting in 26 (42.7%) patients. It was determinate in a total of 28 (62.3%) and indeterminate in 23 (37.7%).

Thus the test is useful as a confirmatory method particularly in military neurology; in addition it is of definite aid as a determinate diagnostic method furnishing new and decisive evidence. A flexible undogmatic individualistic interpretation of this laboratory method, based on statistics and practical considerations is recommended. In no instance should EEG results overrule clinical judgment. It is felt that the group of epileptic patients with normal EEG's and fainters with abnormal EEG's deserve further clinical and laboratory studies.

References

1 Roseman, E.: "The Epileptic in the Army," *Am. J. Psychiat.*, 101: 349-354, (Nov.), 1944.

2 Gibbs, F. A., Gibbs, E. C., and Lennox, W. G.: "Electroencephalographic Classification of Epileptic Patients and Control Subjects," *Arch. Neurol. and Psychiat.*, 50: 111-128, (Aug.), 1943.

3 Romano, J., and Engel, G. L.: "Studies of Syncope. III. Differentiation Between Vaso-depressor and Hysterical Fainting, 3," *Psychosom. Med.*, 7: 3-14, (Jan.), 1945.

4 Finley, K. H., and Dynes, J. B.: "Electroencephalographic Studies in Epilepsy. A Critical Analysis," *Tr. Am. Neurol. Assn.*, 68: 90-95, 1942.

5 Lennox, W. G.: "Real and Feigned Amnesia (Scientific Proof and Relations of Law and Medicine)," *Am. J. Psychiat.*, 99: 732 - 743, (March), 1943.

6 Harty, J. C., Gibbs, E. L., Gibbs, F. A.: "Electroencephalographic Study of 275 Candidates for Military Service," *J. Nerv. and Ment. Dis.*, 96: 435-443, (Oct.), 1942.

7 Robinson, L. J.: "The Electroencephalogram in Some Military and Selective Service Convulsive and Non-Convulsive Problems," *Am. J. Psychiat.*, 102: 305-310, (Nov.), 1945.

8 Schwab, R. S.: "Application of Electroencephalography in the Navy in Wartime," *War Med.*, 4: 404-409, (Oct.), 1943.

9 Solomon, P., Harris, H. I., Wittson, C. L., and Hunt, W. A.: 'Electroencephalogram in Selection of Naval Recruits," *U. S. Navy Med. Bull.*, 41: 1310-1317, (Sept.), 1943.

10 Silverman, D.: "Electroencephalograms in the Army General Hospital," *War Med.*, 5: 163-168, (March), 1944.

11 Engel, G. L., and Margolin, S. G.: "Neuropsychiatric Disturbances in Internal Disease, Metabolic Factors and Electroencephalographic Correlations," *Arch. Int. Med.*, 70: 236-259, (Aug.), 1942.

12 Engel, G. L., Romano, J., and McLin, T.: "Vasodepressor and Carotid Sinus Syncope: Clinical, Electroencephalographic and Electrocardiographic Observations," *Arch. Int. Med.*, 74: 100-119, (Aug.), 1944.

13 Gibbs, F. A., and Forster, F. M.: "Electroencephalographic Studies on Carotid Sinus Syncope," *Tr. Am. Neurol. Assn.*, 67:143-146 (June), 1941.

14 Forster, F. M., Roseman, E., and Gibbs, F. A.: "The Electroencephalogram Accompanying Carotid Sinus Reflex and Orthostatic Syncope," *Arch. Neurol. and Psychiat.*, 48: 957-967, (Dec.), 1942.

15 Romano, J., Stead, E. A., Taylor, N. E.: "Clinical and Electroencephalographic Changes Produced by a Sensitive Carotid Sinus of the Cerebral Type," *New Eng. J. Med.*, 223: 708-712, (Oct.), 1940.

16 Levin, S., Katz, J., and Greenblatt, M.: "An Electroencephalographic Study of Cases with Syncope and Related Disorders," *Am. Jour. Psychiat.*, 102: 301-304, (Nov.), 1945.

17 Jasper, H. H., and Kershman, J.: "Electroencephalographic Classification of the Epilepsies," *Arch. Neurol. and Psychiat.*, 45: 903-963, (June), 1941.

18 Echlin, F. A.: "Electroencephalogram in Epilepsy," *Arch. Neurol. and Psychiat.*, 52: 270-290, (Oct.), 1944.

19 Blier, J., and Redlich, F. C.: "The Electroencephalogram in the Pitressin Hydration Test for Epilepsy," (In print).

Metabolism in Cerebral Malaria

(Practical and Theoretical Considerations)

MASON TRUPP, M.D.
St. Louis, Missouri

Of late malaria has been the subject of many papers. The information gathered by the Armed Service and special groups appointed for its study, through the direction of the Public Health Service and the National Research Council, has contributed a wealth of scientific data dealing with the respiratory metabolism of the malaria parasite, and with advances in laboratory, therapeutic and clinical pharmacological research of this subject. Only during national catastrophic incidents such as the defeat in the Philippines and the British expulsion from Java, Malaya and Burma has this disease received serious attention. Reports dealing primarily with sporadic and isolated cases of cerebral malaria in which the use of such drugs as ephedrine, adrenalin, barbiturates, in addition to quinine and atabrine specifically have been of interest. Little has been written concerning the physiological cerebral functions which become seriously impaired in this disease and frequently result in death. A recent paper described a delayed and interval cerebral syndrome which was noticed among service personnel who had attacks of malaria during war service.[1]

Textbooks of therapy devote scant attention to methods of maintaining physiological cerebral metabolism; yet it is the stability of this function which determines morbidity, life and death in cerebral malaria. Various attempts to induce increased cerebral circulation, through the use of vaso-dilators on the one hand and vaso-constrictors on the other, have produced results which are undependable and so variable that no valid conclusions as to the efficacy of such treatment of encephalitic malaria can be made. Oxygen alone has been used in a small number of cases and results were at times startling, but also in these, no valid conclusions can be drawn.[2] Death occurs too quickly once the diagnosis is made to attribute it to concommitant degeneration of the liver and spleen as was previously thought, since these organs become seriously incapacitated only after protracted involvement.

In 1943-44 in India and Burma the author saw in consultation an extended series of cases of falciparum malaria in which early and profound encephalitic complications were outstanding. The use of an oxygen-nicotinic acid regimen in addition to quinine and atabrine was suggested as a plan of therapy. The first patient so treated was a case of Dr. Porter Mason in September 1943. The results were gratifying. A series of similarly treated cases followed in which results were invariably satisfactory. Rapid reduction in morbidity has been noted in encephalitic malaria in which nicotinic acid and oxygen had been used as a therapeutic adjunct to maintain physiological cerebral circulation and its respiratory substrate control. This paper is presented in an effort to explain in a comprehensive and convenient manner, certain facts of experience in which the regimen was successfully employed, and to present a concept of what is thought to occur during the course of this disease from the cerebrophysiological aspect.

In cerebral malaria, death occurs because the human encephalon is unable to sustain the following disturbances of metabolism:

1. Anoxia.[3,4]
2. Inactivation of oxidative enzyme-substrates.[5,6]
3. Increased viscosity and specific gravity of the blood.[3,7]
4. Altered cellular permeability.[7,8]
5. Loss of integrity of hemato-encephalitic barrier.[3,7,8]
6. Cellular death.

Among the many valid descriptions of the disturbed metabolism observed in cerebral malaria the following concepts must be considered. The anoxic effects of malaria include anemic-anoxia due to deficiency in the transport of oxygen to the tissues because of parasitic destruction of erythrocytes. This conclusion has been established since the produc-

tion of such an anemia is at the expense of the hemoglobin of the erythrocytes and the pigment economy of the parasite, which accounts for the fact that after a single paroxysm of severe estivo-autmnal malaria, erythrocyte determinations may reveal a destruction of as many as one million erythrocytes per cubic millimeter. This pernicious cycle may be continued with each succeeding paroxysm until subsequent erythrocyte counts may fall to a million or less per cubic millimeter.[3,9] There is also an associated stagnant-anoxia due to local embolic or local and general angiospastic circulatory disturbances, with stagnation of blood increased in viscosity, and probably due to embolic pooling of erythrocytes, parasites, pigment, detritus, corpuscle remnants, etc., within the cerebral vascular bed. These embolic phenomena have been confirmed by microscopic study of cortical sections of patients who succumbed to cerebral malaria.[3,9,10]

Patients with encephalopathic malaria, in the presence of the above described anemic and stagnant anoxia, and an incidental hyperpyrexia, develop an intracellular oxygenation defect with concommitant inactivation of oxidative enzyme substrate systems necessary for preservation of normal cellular permeability. Present theory indicates that pigment, liberated from invaded and destroyed erythrocytes, spreads over and tends to become adherent to other uninvaded erythrocytes and to the endothelial walls of the cerebral capillaries. Pigment adhering to erythrocytes and to the endothelial cells of capillary sections alters the electro-potential normally present on these cellular surfaces and promotes rouleau formation and other embolic phenomena. Coated erythrocytes and coated capillary walls prove a serious burden to an already flagging cerebral metabolism. The presence of erythrocytic remnants, pigment, and malarial toxins increases the viscosity and specific gravity of cerebral blood and contributes to decreased cerebral blood flow.[3,11] This chain of circumstances, unless halted, soon disorganizes the mechanisms for maintaining physiological cerebral metabolism and its oxidative substrate control. The oxygenation defect leads to altered cellular permeability and loss of integrity of the blood brain barrier.

Evidence that this is taking place during life may be substantiated by studying the fundi of patients developing the ocular complications of cerebral malaria. Histologic studies of the eyes of patients who die from cerebral malaria ...."show retinal hemorrhages, overfilled capillaries, ampulliform dilation of the veins, edema of the vessel walls and lymph spaces, and papillary and peripapillary edema. The erythrocytes containing the plasmodium lay in the arteries and capillaries, while the larger veins contain pigment filled leukocytes; ectasia of the choroidal capillaries is produced by the thrombi which are present."[10]

The blood brain barrier of man has always proved fragile to the march of events described in cerebral malaria. This is not always true of other species susceptible to malaria. Attention is called to Rigdon's important studies which would indicate that the hemato-encephalitic barrier of the duck is more resistant than the barrier of man or monkey.[12] Experience indicates that nicotinic acid aids in oxidizing the elements of toxic pigment degeneration, dissolves these from cell surfaces, supplements oxidative exchanges across cell membranes, restores physiological permeability and produces an adequate cerebral blood flow. This is advanced as the pharmacological action of nicotinic acid in the treatment of cerebral malaria.

Use of quinine-epinephrine mixtures have frequently been mentioned in literature. Hanzlick and Cutting,[13] call attention to the fact that intravenous injection of quinine is probably contra-indicated in the presence of severe shock especially hemorrhagic, pulmonary edema, cardio-vascular disease, cyanosis, severe anemias, pregnancy and possibly other conditions. Epinephrine, these authors caution, is not to be used routinely and is probably contra-indicated in shock and pulmonary edema. They warn that with the use of epinephrine the blood pressure response should be watched carefully and the administration discontinued if the blood pressure rises above 160 or the pulse rate is much accelerated, or if other untoward symptoms appear. It would appear in the author's observation that should cases of cerebral malaria be selected for treatment with quinine-epinephrine mixtures on the basis of the

absence of the above cited contra-indications, few cases of cerebral malaria would receive such treatment, for most cases of cerebral malaria develop early marked cyanosis, shock, anemia, rapid pulse rate, and are deeply comatose and in extremis often before the diagnosis has been established. Experience shows that cerebral malaria is rapid in onset and life is seriously embarrassed by all the above mentioned exigencies.

It is emphasized that the nicotinic acid-oxygen regimen should be considered a composite one. Oxygen therapy alone has a tendency to result in constriction of smaller arterioles and thereby decreases cerebral blood flow. It is further recommended that in the treatment of cerebral malaria the use of nicotinic acid and oxygen be started at the onset and that nicotinic acid be continued after curtailment of oxygen administration in order to maintain the integrity of the oxidative enzymes substrates which have been reconstituted as the result of such therapeutic management. Nicotinic acid used in conjunction with oxygen therapy induces an optimum cerebral oxygen consumption and an increased blood flow.

Nicotinic acid increases cerebral blood flow[14,15] and aids in restoration of respiratory enzyme systems.[5] It is suggested that massive paroxysmal destruction of available nicotinic acid during the phase of parasite multiplication may represent one of the factors operating during the course of this disease since the action of nicotinic acid is thought to occur on cellular surfaces. Because of this, its use is advised in all severe falciparum infections even though cerebral symptoms have not become seriously manifest. Administration of nicotinic acid should be continued as long as mental manifestations exist, such as altered memory, disorientation, delirium, coma, headache, mania, or depression. Up to 600 mgm. may be given intravenously in twenty-four hours or by mouth in the same dosage. When nicotinic acid is not available, 1000 mgm. nicotinic-acid-amide per day may be given by mouth. Nicotinic-acid-amide does not induce an increase in the cerebral blood flow, but substantially aids reconstitution of respiratory enzymes and thereby maintains physiological cerebral metabolism. In 1944 Most and Meleney described a case of cerebral malaria in which intravenous injection of nicotinic acid restored consciousness immediately.[15] These authors recommended its use because of rapid selective stimulation of cerebral blood flow, which is consistant with the author's experience in a long series of cases. Nicotinic-acid-amide has also markedly reduced the morbidity of uncomplicated falciparum malaria. Since this drug exerts no selective stimulation to cerebral blood flow, its single role in reconstitution of respiratory enzymes is important.

Fitz-Hugh, Pepper and Hopkins[16] describe the development of sudden severe cerebral symptoms one to three days after admission with, and routine treatment of, what appeared to be ordinary malaria. Silverman, Ceithaml, Taliaferro and Evans[6] have demonstrated a direct correlation between parasite surface area and various metabolic activities. On the basis of surface area calculations the respiration of P. gallinaceum was found to be about seventy times that of the normal chicken erythrocyte. Recent investigation indicates that quinine itself may have some effect on enzyme systems or components of enzymes common to both respiration and glycolysis. It is possible that quinine and atabrine may become encephalo-toxic in patients in whom nicotinic acid is paroxysmally destroyed during parasite multiplication and this may explain a situation which these authors[16] indicate lacks interpretation. Thus it would appear that the malaria parasite invades its host seeking both respiratory pigments (hemoglobin) and its associated primary enzyme (nicotinic acid). It is suggested that the therapeutic index of quinine, a protoplasmic poison, may be extended by the addition of nicotinic acid to the treatment of malaria. Nicotinic acid may be used to reduce the toxicity of quinine when it is used in large doses or when a debilitated patient appears excessively sensitive to quinine.

The amount of oxygen given will depend on individual response, certainly up to the time that patient is well orientated and free of headache. Sudden withdrawal may be followed by collapse which calls for resumption of oxygen therapy. Oxygen may be administered by nasal catheter, tent, or mask, the latter method being preferable. With the

use of a nasal catheter, the oxygen flow should be at a rate of six liters per minute. Use of the B.L.B. mask is recommended as the most suitable method. Since there is a tendency for carbon dioxide to accumulate in this mask, manipulation of the rebreather bag will exhaust the excess carbon dioxide and prevent discomfort due to hyperventilation.

It should be remembered that quinine is neuro-toxic, viz., eighth nerve deafness, peripheral neuritis, involvement of all tissues of the eyes, the optic nerve, its vascular components, its specialized adventitia, and other cerebral connections. Quinine amblyopia is indicative of perfusion of the optic nerve by a chemical in quantity which ordinarily does not pass the hemato-encephalic barrier. Evidence of any of the above chemical complications indicates altered cellular permeability and loss of integrity of the blood brain barrier which needs reconstitution.

Use of quinine and atabrine are mentioned to signify unequivocal emphasis to the specificity of these drugs, and to remind one that it would be folly to attempt treatment without such important drugs (often in parenteral solutions) in the armamentarium of those who treat malaria. Recent investigations would indicate the necessity of directing treatment in addition to the specific disrupted metabolism which is observed in these cases and which has been described herein.

Quinine and atabrine are therapeutic agents for the treatment of cerebral malaria and should always be used in the treatment of this disease. Encephalic malaria is frequently rapid in onset with delirium or coma, and death often ensues without return to consciousness. Diagnosis in these cases should be accurately determined by parasite demonstration. It has been the experience of the author to see several cases treated for cerebral malaria, in endemic areas which at postmortem showed no evidence of cerebral disease. It is also necessary to keep in mind that there are also non-malarial encephalitis. Quinine is not the drug of choice in such entities. Encephalitic malaria has frequently defied accepted medical management. The adjuvant regimen herein described has consistently met with expedient and profitable efficacy. Although it is true that daily atabrine prophylaxis will almost always prevent blackwater fever and cerebral malaria, such a regimen actually is rarely used except for strategic military operations.

Case Reports

Case No. 1: N.M.S. became ill with fever on September 6, 1943 and was treated with quinine at a nearby sick bay for several days before admission to the hospital. His original complaints consisted only of fever and malaise. On September 11 he suddenly became comatose and had generalized muscular twitchings. He was given 10 grains quinine dihydrochloride intravenously and seemed to improve. However, the next morning his coma and general muscular twitchings recurred and he was brought to the hospital for further care. On admission the patient was comatose, cyanotic, pulse 160 and feeble, blood pressure was 100/60. The patient was given 100 mg. of nicotinic acid every four hours for six doses and continuous oxygen therapy with a B.L.B. mask for twenty-four hours. The cyanosis cleared in three or four minutes and in about fifteen minutes the patient could be roused to a point where he responded to direct questioning and was able to take medication by mouth on instruction. By this time his pulse was 90 and of good volume, blood pressure was 112/70. After about twenty-four hours of oxygen, the mask was removed as the patient was completely clear mentally and seemed to feel all right. However, in about an hour he became somnolent but not comatose. The oxygen was resumed for another twelve hours after which the patient was mentally clear and remained so. During the first twenty-four hours of the patient's treatment in the hospital he also received 6 mg. of vitamin K in an attempt to prevent multiple punctate cerebral hemorrhages. This was discontinued when it was thought that it might possibly give rise to further embolic phenomena.

Cases Nos. 2 & 3: R.M.S. and H.I.R. are reported together as their clinical pictures and response to therapy was very similar. Dr. Porter Mason treated these cases which he classified as precerebral cases, because it was considered that they had signs of cerebral irritation. Both patients had infections with P. falciparum and their chief complaints were severe headache; and slight mental confusion was discovered on questioning each about his history. There was no evidence of coma or cyanosis. Due to intractable headache (no relief with 1 gr. codeine) and apparently slight mental confusion, it was decided to institute the oxygen-nicotinic acid therapy. Both patients were given 100 mgs. of nicotinic acid q.i.d. and oxygen therapy for one hour q.i.d. The headache and mental confusion cleared after the first hour of treatment. The therapy was continued for two days with this regimen with no recurrence of these symptoms. Both patients experienced rapid relief from

symptoms and made uneventful recoveries and were discharged on the thirteenth hospital day.

Comment

The physiological approach to the malarial problem presented above is based on the principal that the parasite competes with the host for certain products and factors of tissue metabolism advantageous to both. The capacity of the host to make an adequate immunological response during this competitive phase, complicated by the introduction of a chemotherapeutic agent which is highly toxic to the parasite and moderately toxic to the host may necessitate reinforcement of biological functions of the host by the introduction of specific growth substance adjuvants. Since the respiratory avidity of the parasite is seventy times that of the normal erythrocyte, supplementing oxygen to the host would be indicated. The morbidity of cerebral malaria appears to be an encephaloanoxic entity associated with rapid and profound depletion of respiratory enzymes and specific growth factors producing a profound disorganization of cerebral metabolism. It is unfortunate that quinine has a profound inhibitory effect on oxygen intake and glucose utilization, since the metabolism within the brain is almost exclusively limited to carbohydrate oxidation unparalleled by any other body tissue.

The author has had in a few isolated instances the opportunity to observe patients survive malaria paroxysms and parasitemia to disappear in cases in which nicotinic acid was the only drug administered, and it would seem that disorganization of metabolism was prevented by use of the regimen without having to resort to either quinine or atabrine. It has been noted that various serologic antibodies, including precipitins, agglutinins and complement-fixing antibodies appear during malaria.[17-24] The manner in which the pharmacological action of nicotinic acid supplements the immunological response of the host merits further investigation.

Summary

1. A concept of the disturbed metabolism of cerebral malaria is presented.

2. The oxygen-nicotinic acid regimen is discussed as an adjuvant to specific treatment of cerebral malaria.

References

1 Zeligs, M. A.: "Management of Chronic Malaria Between Attacks," *J.A.M.A.*, 129: 796-798, (Nov. 17) 1945.
2 Unclassified communication from the Office of the Theater Surgeon, Rear Echelon Headquarters, U.S.A.F., C.B.I. and concerns the findings of the 20th General Hospital where a special ward had been set up to study the therapy of cerebral malaria.
3 Rigdon, R. H.: "A Consideration of the Mechanism of Death in Acute Plasmodium Falciparum Infection, Report of a Case," *American Journal of Hygiene*, 36: 272-274, 1942.
4 Rigdon, R. H., and Stratman-Thomas, W. K.: "A Study of the Pathological Lesions in P. Knowlesi Infection in M. Rhesus Monkeys," *American Journal of Trop. Med.*, 22: 329-339, July 1942.
5 Koser, S. A., Baird, G. R.: "Bacterial Destruction of Nicotinic Acid," *Journal of Inf Diseases*, 75: 3, p 261, 1944.
6 Silverman, M., Ceithaml, J., Taliaferro, L. G., Evans, E. A. Jr.: "The In Vitro Metabolism of Plasmodium Gallinaceum," *Journal of Inf. Diseases*, 75: 3, p 225, 1944.
7 Landis, E. M.: "The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to the Plasma Proteins," *American Journal of Physiology*, 83: 528, 1927-28.
8 Krogh, A.: "Anatomy and Physiology of the Capillaries," *Yale University Press*, New Haven, 2nd Edition, 1929.
9 Strong, R. P.: "Stitt's Diagnosis," *Prevention and Treatment of Tropical Diseases*, p 49 and p 57, 1942.
10 Bothman, L.: 1943 Year Book of Eye, Ear, Nose and Throat: *"Eye Complications in Malaria,"* pp. 7-27.
11 Knisely, M. H., Stratman - Thomas, W. K., Elliott, T. S.: "Observations on Circulating Blood in the Small Vessels of Internal Organs in Living Macacus Rhesus Infected with Malaria Parasites," (Abst.), *Anat. Rec.*, 79: 90, 1941.
12 Rigdon, R. H.: "A Pathological Study of the Acute Lesions Produced by Plasmodium Lophurae in Young White Pekin Ducks," *American Journal of Tropical Medicine*, 24: 6, p 371 and p 377.
13 Hanzlik, P. J., Cutting, C. C.: "Clinical Trials with Quinine - Epinepherine Intravenously," *J.A.M.A.*, 199: 1241, 1946.
14 Aring, C. D., Ryder, H. W., Roseman, E., Rosenbaum, M., Ferris, E. B. Jr.: "Effect of Nicotinic Acid and Related Substances on the Intracranial Blood Flow of Man," *Archives of Neurology and Psychiatry*, 46: 649, (Oct.) 1941.
15 Most, H., Meleney, H. E.: "Falciparum Malaria," *J.A.M.A.*, 124: 2, p 75, 1944.
16 Fitz-Hugh, T. Jr., Pepper, D. S., and Hopkins, H. U.: "Cerebral Form of Malaria," *Bulletin of U. S. Army Medical Department,"* 83: 1-22, 1944.
17 Coggeshall, L. T.: "Humoral Immunity in Malaria," In Moulton: A Symposium on Human Malaria, *AAAS, No. 15*, Sect. 6: 250, 1941.
18 Coggeshall, L. T.: "Immunity in Malaria," *Medicine*, 22: 87, 1943.
19 Dulaney, A. D., and Stratman-Thomas, W. K.: "Complement Fixation in Human Malaria; I. Results Obtained with Various Antigens," *Journal of Immunology*, 39: 247, 1940.
20 Eaton, M. D., and Coggeshall, L. T.: "Complement Fixation in Human Malaria with an Antigen Prepared from the Monkey Parasite Plasmodium Knowlesi," *Journal of Experimental Medicine*, 69: 379, 1939.
21 Kingsbury, A. N.: "Some Investigations of

Malarial Fevers. IV. The Complement Fixation Reaction," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 20: 359, 1927.
22 Kligler, I. J., and Yoeli, M.: "The Diagnostic and Epidemiological Significance of the Complement Fixation Test in Malaria," *American Journal of Tropical Medicine*, 21: 531, 1941.
23 Stratman-Thomas, W. K., and Dulaney, A. D.: "Complement Fixation in Human Malaria. II. Diagnostic Application," *Journal of Immunology*, 39: 257, 1940.
24 Taliaferro, W. H.: "Immunity in Malaria," *A. J. Clic. Pathology*, 14: 593, 1944.

Behavior as a Measure of Occupational Fitness

STEPHEN WEISZ, M.D.
Galveston, Texas

On meeting people in everyday life one automatically registers some sort of impression of them. However vague it may be, a person would usually be able to formulate this impression by the description "a likeable chap," "a personable fellow," and so on. Repeated meetings with the same individual will gradually establish a certain pattern of behavior which we come to associate with him. Behavior represents the conduct, manners and habitual responses of a person and also the motives as reflected in his acts. The psychiatrist's chief interest is to find out why a person has developed in a certain way and why he behaves as he does.

In our complex society, every individual grows up in and is part of a group, going through a process of moulding, both by his own experiences and by the transmission of the experiences of his parents, teachers and others about him. The good "breaks" one has had in life, the tough luck and the golden opportunities will establish themselves as sort of focal points to which a person frequently refers in narrating his life history. Social relationships from the time of birth, meanwhile also furnish the opportunity for transmission to the growing individual of personal bias and grudge. Our evaluation of life will largely depend upon our own experiences and the teachings we happen to receive. The function of education is to prepare a person to take his place in society and to help him to adjust to his surroundings and circumstances.

It is natural for man to live in a group. We are all part of one. It should be kept in mind, however, that in human society there are numerous groups and that membership will vary according to the constitution of the particular organization. Association of men on the basis of religion in church membership, or by being of similar race, or for purely social reasons as in club membership, will bring people together in varying combinations. Depending upon the requirement of the membership, an individual will have a different role in the framework in each association. Membership in several groups are often interrelated as for instance, by sex, color and family. On the other hand some affiliations are relatively independent, as church membership.

Industrial behavior is based on, and controlled by membership in the industrial group. There the productivity of a man is the chief criterion for his eligibility. The best adjusted to the industrial group and the most efficient is the man who is well trained for his job and who, in addition, is capable of establishing a stable personal relationship with his co-workers. Industrial behavior is, therefore, behavior of a specialized kind, referring primarily to the occupational fitness of the worker.

It is to the advantage of industry to be acquainted with the various sources which might interfere with the occupational fitness of the worker. Roughly speaking, there are two general sources of such interference. One originates with personal liabilities. A worker may have a defective intellectual endowment. Such a person often becomes the target of jokes, is slow witted, does not catch on, and cannot do a job although shown repeatedly. In spite of best intentions such a man cannot perform satis-

factorily and may respond with unhappiness or dissatisfaction. A number of personal factors have a bearing upon the worker in relation to his employment. Unhappy home life, stresses in the family situation, sexual difficulties, may make a person restless, anxious and fidgety. The worker may become so absorbed in his personal problems that he cannot hold his attention on the job. Some take to alcohol as a way out of the difficulties. Some complain of fatigue. Various neurotic symptoms may be manifested which may eventually lead to illness and absenteeism. In an appropriate personality such a state of inner tension may express itself in repeated accidents. Underlying all of these personal factors of industrial mal-adjustment is the division of the attention of the worker between his own problem and his work. He cannot concentrate on his work and maintain his efficiency.

The second source of disturbance of occupational fitness stems from what one might call faulty group adjustment. It takes many forms. One may mention as an example, the inadequate preparation of a man for his role in society due to pampering and over-protection at home or simply because of inadequate schooling. Rigid transfer of patterns adopted in childhood and found useful within the framework of the family may not be suitable in industrial relationships. Whatever the basis of the difficulty such a person ofttimes is unhappy and probably out of place. To cite a few examples: the practical joker who wastes everyone's time, including his own, and may cause an accident; the fault finder and griper; the chronically dissatisfied person, sullen and rebellious and a trouble maker. There is the aggressive, know-it-all who butts into everyone's business and gives advice without being asked. Then there is the shy, sensitive, pessimistic individual who makes mountains out of molehills, who hides his light under the bucket all of the time, who is afraid of responsibility and who, though smart, does not reach the level of his potential abilities. Mention should also be made of the handicapped person, for instance, one suffering from epileptic seizures. Unless he is accepted in the group it will work a hardship for all concerned.

These mal-adjustments are acquired and can be straightened out to a large extent. For industry, primarily interested in the smooth operation of the plant, it is important to know how to recognize them. Many are not difficult to identify. A fall in the efficiency of the worker, unexplained changes in work habits, fluctuations in performance are manifestations easily recognized. Another method of detecting these forms of mal-adjustment is through a thorough work history on hiring an applicant. However, this may not always be reliable. It cannot be expected that a person who has been let out for inefficiency or other personal reasons will relish describing the circumstances. Common sense dictates that he would gloss over that part and embellish his achievements.

The use of tests of some sort is helpful in discovering these idiosyncracies. The performance of a man under test situations is a delicate evaluation and the examiner must be well versed both in the testing and in the appraisal of stagefright in such situations. The Cornell Selectee Index has been suggested for use as an occupational questionaire. It consists of occupational questions, of questions referring to self-evaluation and the so-called stop questions or inventory which are made up in a way that any unusual answer may cause the examiner to stop, look and listen. More time can then be allowed for that individual. The application of the Rorschach for the purpose of group testing has been introduced; final evaluation is pending.

The simplest, although more time consuming method is the old fashioned placement interview where one sits down and chats with the applicant. This is very much the way that a psychiatrist proceeds with a patient. It is informal and yet can be very informative. Watch the appearance of the person, how he sits on the chair, how he fidgets, how he trembles, or how self-assured he looks. One can learn a lot just by observing. For a topic of conversation one may talk about his hobbies. According to our culture everyone is supposed to have one. If he has one, what is it? Why? If he doesn't have one can he give a reasonable explanation why not? Most people without a hobby have quite acceptable reasons. Then one may switch to a discussion of current events to hear the opinions of the

worker on things in which he is not personally involved so as to estimate his judgment and intelligence. By this time the applicant may have relaxed. At any rate, some sort of rapport or the lack of it becomes apparent. One may then approach the most important question, namely, the vocational interests of the person. What does he want to do? Had he done it before? One should try to find out the reasons for the particular interest. Is it genuine? Does the applicant know what he is talking about, or is his explanation superficial and vague? Are his answers indifferent? Does his talk indicate a steady interest or a shifting one? Was he forced to take the job by circumstances or by preference? Or does it not make any difference to him what kind of job he has? Finally, the conversation should be gradually shifted to the applicant's previous work and physical history so as to find out about his previous employment and physical health.

Industry often asks the question, what to do about an occupationally mal-adjusted worker. To begin with it should be said that abnormal behavior is not necessarily prohibitive of successful employment. We have seen discharged patients still manifesting signs of their nervous disorders, going about their daily jobs, or persons, obviously odd, performing responsible jobs. In this connection intelligent tolerance is required. As long as a man does what he is supposed to do in industry one should learn to close an eye to his idiosyncrasies unless they are disturbing to the welfare of the group. Employment means much to these people and they will put up with a great deal to be again self-supporting.

It is easy to say, put the man in the right place. This, however, is not so easily done. One can at least try to make everyone a responsible member of the group. A successful worker is not a griper. Encouragement and praise pay dividends. Advisors can help and council in individual problems. As for the group, one should try to build up a group consciousness. Nothing is more appreciated than loyalty. The Army has done a splendid work in building up esprit de corps. It is true industry is motivated by other considerations than the Army, yet if the workers understand and feel that they have a part in the considerations of management, that their jobs are important, they will respond. This is probably one of the most important jobs management can perform for the workers. The aim should be for an interrelated whole, a group, instead of an aggregation of individuals.

REFERENCES

1 Bloomfield, J. J.: "Labor-Management Relationships in Industrial Health Problems," *J.A.M.A.*, 128: 639-643, 1945.

2 Burlingame, C. C.: "Industrial Psychiatry—Facts —Not Fancy," *Bull. Mass. Soc. Ment. Hyg.*, Feb. 1945.

3 Mittlemann, B., et al: "Detection and Management of Personality and Psychosomatic Disorders Among Industrial Personnel," *Psychosom. Med.*

4 "Readjustment to Civilian Jobs," Report on Neuropsychiatric Problems Relating to Employment in Industry, *Bull., Nat. Asso. Manufact.*, New York, 1945.

5 Solby, B.: "The Mental Hygiene of Industry and Reconversion," *Mental Hyg.*, 29: 353-370, 1945.

6 Terhune, W. B.: "Mental Hygiene in Industry," Publ. No. 4, *Silver Hill Found. for Treatm. of Psychoneur.*, New Canaan, Conn.

7 Weider, A., et al: "The Cornell Selectee Index," *J.A.M.A.*, 124: 244-248, 1944.

Neurological Clinical Pathological Conference

of the
Cincinnati General Hospital
CHARLES D. ARING, M.D., *Editor*

Case No. 197238

Presentation

A 34 year old colored man was transferred from another hospital on September 27, 1944. The patient was said by his wife to have consumed ½ to 1 pint of whiskey daily for several years. In early May he suffered the onset of periodic, severe, generalized headaches lasting for three to twelve hours. During these periods of pain he had blurred vision "as if a film of water was over both eyes". In the earlier attacks he could not tell colors, later objects were difficult to delineate during the attacks. The periodic headache and blurred vision became more prolonged and severe until August 8 when he was brought home from work with the story that he had suddenly gone blind. Then he could see nothing; it was determined that he could not distinguish between light and dark.

At about the same time in August he noted weakness in the legs, slight diminution in hearing and numbness and tingling in the lower, and later in the upper extremities. About this time he also became untidy and occasionally talked incoherently. He had lost much weight with the present illness.

In early August he applied for treatment at the office of a neurologist and the findings were much as noted in later examinations. The blood pressure was normal, the lower halves of the visual fields were obliterated, there was slurred speech, and ataxia. The patient complained of burning in the hands and difficulty in voiding; complaints about "odors" were vague.

The following neurological abnormalities were found on September 15. He was talkative and euphoric, his speech was somewhat slurred. He would suddenly grab his feet and rub them as if in pain, he stated that they were numb. He had a vacant stare and appeared to be blind; he was unable to count fingers though he could identify large objects but not their color. There was weakness in converging the eyes, and slow horizontal nystagmus. Hearing was slightly impaired and speech was explosive and slurred. There was a lag between the request for and the performance of a movement. Terminal tremor was found in tests of coordination. He walked on a broad base, occasionally staggering. The deep reflexes were hyperactive, the abdominal and cremasteric reflexes absent.

Increasing weakness, urinary incontinence and mental confusion supervened in late September. Cramps in the feet and calves became a frequent symptom. On September 29 he was disoriented and confused; he talked incessantly and appeared to be able to see the light of a strong flashlight placed directly in front of the eyes. The right pupil was 6 mm., the left 4.5 mm. in diameter. They reacted slowly, through a fair range. The reflexes were as noted previously. He thought that he could not use the left hand, but it appeared to be as strong as the other in the usual tests for motor function.

He had to be given considerable paraldehyde throughout the first week in October, since he was restless, resistant and noisy. On October 7 he cleared a bit mentally, as he was wont to do periodically throughout his hospital stay. Weakness was now apparent in the left upper extremity and he complained of pain therein. He paid no attention to objects placed in his left hand.

On October 20 he would not blink if a flashlight were held at a distance of 2 cm. from either pupil; the pupils reacted to direct and consensual light. Ankle clonus was obtained bilaterally. He moved his right extremities but seemed to have forgotten his left extremities, which usually seemed insensitive. The left lower portion of the face had less expression than the right. He was alert, spoke unintelligibly for the most part, and seemed to be suffering from receptive and expressive dysphasia. A few days later his speech was clear and temporarily he spoke

rationally and was oriented.

He developed pneumonia on October 27 and despite specific and supportive therapy, he maintained a high fever. He was comatose from October 27 until his death on November 8th.

Laboratory Data: The blood pressure was abnormal throughout the hospital course, the systolic pressure ranged around 170, the diastolic around 120 mm. With the development of pneumonia, sugar and albumin were found in the urine and the white blood count rose to 26,000. The blood Kahn was repeatedly negative. The blood urea nitrogen was normal until October 27 when it was 100 mg.%, thereafter it was determined to be 85, 25, 24, 21, 21, and 30 mg.% on every second day. Roentgen studies of the chest and head were normal.

An electroencephalogram on October 23 revealed a dominant record of a somewhat irregular, slow rhythm, the frequency 8 per second. It was thought to be consistent with brain damage of fairly long duration, which was apparently active. There was no localization and blindness could not be examined for adequately.

Seven cerebrospinal fluid analyses were done.

Differential Diagnosis

Dr. Joseph P. Evans: I have found this case difficult. I will go through the pattern of my thinking, which I hope has resulted in arrival at a reasonable conclusion. The patient was a young man who had a partiality toward alcohol, which is one factor we may have to consider. In May 1944 he began to have headache, which was intermittent and quite severe; a story we occasionally hear with increased intracranial pressure, a concept that I had to abandon later. Such headache is sometimes associated with visual disturbances called "black-outs," temporary, complete loss of vision accompanied by papilledema. Obviously, that was not the case here.

A second cause of intermittent headache which may be associated with visual difficulty is migraine, which may be dismissed as a possibility in this patient. This man had neither increased intracranial pressure nor migraine, but some sort of reversible process; for although blind in August, when seen later by a neurologist he had some preservation of vision in the upper fields. The disturbance in vision indicates that there was a lesion between the geniculate bodies and the striate cortex because of the fact that the light reflex was preserved, though somewhat impaired.

In August he noted weakness in his legs, some diminution in hearing and numbness in all of the extremities; mental disturbances were observed, evidence of a diffuse lesion perhaps in the cerebrum but possibly in the brain stem as well. The slow horizontal nystagmus suggests localization in the stem. The hyperactivity of the deep reflexes and absence of skin reflexes suggest involvement of the pyramidal pathways. I think the fact that he was noisy and difficult to manage does not help much except to indicate a diffuse lesion.

One of the more sharply localizing signs was the denial of the left extremities (Gerstmann's syndrome) indicative of a right parietal lobe lesion. The speech disturbance was suggestive of a true dysphasia, and presuming that he was right-handed, this finding implicates the left hemisphere, further evi-

Date	*I. Pressure*	*CC Removed*	*F. Pressure*	*Color*	*WBC*	*RBC*	*Protein*
8/28	95	..	...	Water	1	1	27
9/15	200	15	150	Water	0	....	28
10/2	230	8	120	Blood (Traumatic)	45	1250	64
10/5	190	10	180	"	22	6300	120
10/6	70	10	...	Sl. Xantho.	7	1536	50
10/24	165	10	40	Water	4	1	24
11/6	160	12	65	Water	2	130	11

Sugar and chloride determinations, colloidal gold curve, and Wassermann tests were normal with each specimen.

dence of diffuse disorder.

He had lost weight, which brings forward the consideration of neoplasm. The arterial hypertension appears to have developed during the course of his illness, as a secondary phenomenon.

The cerebrospinal fluid studies are of considerable significance. They indicate rather little evidence of increased intracranial pressure and the fluid was clear throughout with the exception of the traumatic taps. I should judge that after the first traumatic tap there was continued bleeding in view of the fact that the second protein determination was higher than that of the fluid obtained at the first traumatic tap. The normal white blood cell count in the cerebrospinal fluid would seem important in the differential diagnosis.

I am left with the belief that this patient had a diffuse lesion involving the right and left cerebral hemispheres as well as the brain stem and the pathways to and from the cerebellum. Furthermore, there was some evidence that the process was a fluctuating one before it caused death.

In seeking the etiology one may use the academic technique and think of categories of disease: congenital, developmental, traumatic, infectious, toxic, metabolic, vascular, neoplastic and degenerative. There is no reason to consider congenital or developmental defect, and there is no story of trauma. This doesn't seem to be the picture of subdural hematoma, the process is too diffuse.

There is no frank evidence of infection; of the bizarre types one thinks of encephalitis and yeast infection. There is no reason to suspect toxins. Could this be a metabolic disorder? There is a suggestion certainly that vitamin deficiency may be playing a role in relationship to the sensory symptoms in the limbs, but it is impossible to explain the entire picture on this basis. Nor does the story suggest to me a demyelinating process or a degeneration such as pre-senile dementia. Neoplasm may, I believe, be ruled out because the process is so widespread. I considered diffuse leptomeningeal invasion (sarcomatosis of the meninges), but there are too few signs to support this diagnosis. The possibility of sarcomatous invasion penetrating the cerebral perivascular spaces seems worth mentioning.

Finally to consider vascular disease, one thinks of syphilis, but there is no history of it and there is considerable serological evidence against it. Hypertension we have mentioned before; it developed after the establishment of the disease syndrome. One thinks about an arteriosclerotic process, for which there is very little evidence. We must remember that the patient was only 34 years of age.

Other possible vascular diseases include periarteritis nodosa which must be considered in view of the sensory symptoms in the limbs and the hypertension. The disease which I think really is the answer to the problem is cerebral thromboangiitis obliterans. This is an attractive diagnosis because the process seems primarily vascular, it occurred in a young individual, and there was some variability in its course. Cerebral Buerger's disease could account for all of the signs and symptoms which our patient had. My diagnosis is cerebral thromboangiitis obliterans with periarteritis nodosa as a second possibility.

Dr. Charles D. Aring: I am comforted by Dr. Evans' discussion since we on the service had reasoned in practically the same manner. The patient was presented at the clinical conference of October 7, 1944, just a month before he died. This conference was recorded extraordinarily well by Dr. Richard McKay; after discussions by Drs. Vonderahe, Scheinker, Salzer, Rosenbaum and myself, I summed up the problem as follows: "In summary, the cerebrospinal fluid studies up to now are not helpful in differential diagnosis. The patient is a heavy user of alcohol, however, he has been doing hard work for a year and a half so that he must have been eating well. The hyperiesis is worrisome but has remained below the levels that we have come to expect in the young negro with hypertensive brain disease. It is unlikely that he was exposed to toxins in his work at the Wright Aeronautical Corporation.

"His first symptoms were visual in origin; he could not tell colors, but could recognize objects. The lesion has got to be between the geniculate bodies and the occipital lobes; something began in the occipital region bilaterally and has spread forward. On the basis of a bilateral, posteriorly placed lesion spreading forward one can account for all of the findings: the visual disturbance, paresthesias,

reflex changes and weakness. The differential diagnosis is between a vascular disorder such as Buerger's thromboangiitis obliterans, and diffuse neoplastic or demyelinating lesion."

Student: Why wasn't multiple sclerosis considered?

Dr. Aring: We thought of Schilder's disease which is a demyelinating encephalopathy. The cerebrospinal fluid did not favor the diagnosis of disseminated sclerosis neither was it against it. The greatest objection to the diagnosis of disseminated sclerosis was the visual disorder which progressed to nearly complete bilateral blindness, which is practically unknown in disseminated sclerosis. Another objection to the latter diagnosis was the fact that it was possible to localize the lesion, the lesion was not disseminated in type.

Student: How often have you seen Schilder's disease at this hospital?

Dr. Aring: Never.

Discussion of Pathology

Dr. I. Mark Scheinker: The autopsy was limited to the brain. There were no signs of increased intracranial pressure such as flattening of the gyri or narrowing of the sulci, there was no uncal herniation. The splenium of the corpus callosum was somewhat enlarged and there was a slight cerebellar pressure cone.

Coronal sections revealed a neoplastic process widespread in the posterior half of the cerebrum bilaterally. The posterior half of the corpus callosum was widened, discolored and partly degenerated; the process extended more anteriorly in the white matter of the right parietal lobe where it was cystic (Fig. 1), than on the left side.

A hemorrhagic lesion destroyed the lenticular nucleus, the tail of the caudate nucleus and the white matter contiguous to these gray masses on the left (Fig. 2). On the same side the tumor completely destroyed the optic radiation (Fig. 1); on the right this structure was partially involved. The white matter of the entire left occipital lobe appeared to be implicated. The brain stem at midbrain, pontine and medullary levels appeared grossly to be normal.

Sections for microscopic study were taken from several areas of both occipital, parietal and temporal lobes and from the corpus callosum, hypothalamus, optic chiasm, and brain stem. Under low power magnification the structure of the tissues appeared fairly uniform in all sections. Except for a striking

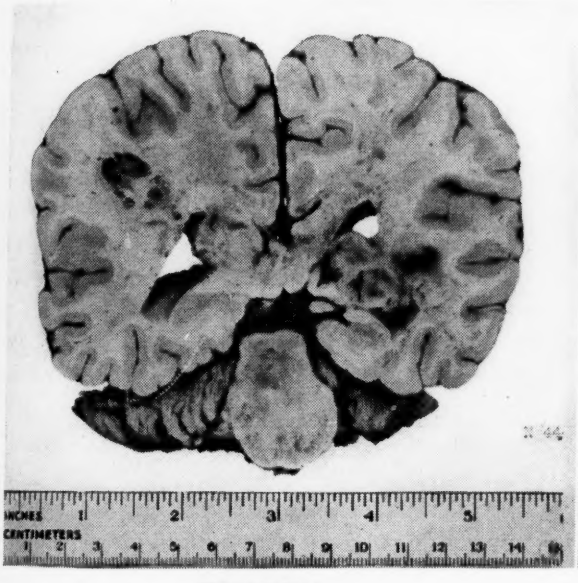

FIGURE 1

Figure 1: A coronal section of the cerebrum transecting the pineal gland, to illustrate the widespread nature of the neoplasm, grossly obvious in the white matter of the right parietal lobe, in the corpus callosum and in both occipital lobes.

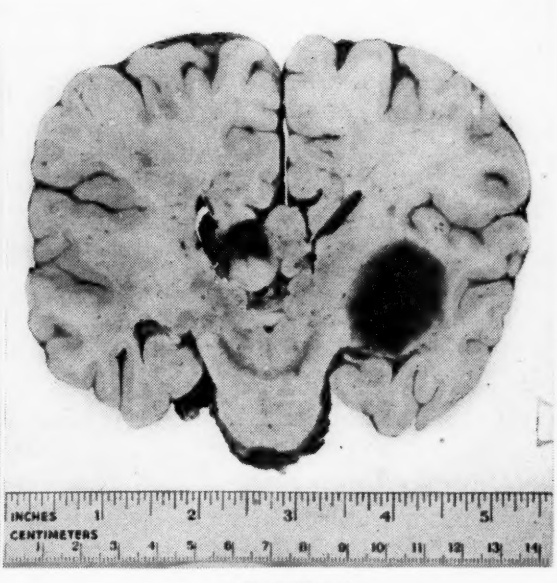

FIGURE 2

Figure 2: A coronal section of the cerebrum at the level of the tail of the caudate nucleus and the substantia nigra, to show neoplastic-hemorrhagic destruction of the posterior extent of the left lenticular nucleus and the contiguous white matter. Note the neoplastic destruction of the corpus callosum, and also the pathologic process just visible in the white matter of the right parietal lobe.

cellularity of the areas involved in the lesion, the general structure of the nervous tissue appeared relatively well preserved. Under high power magnification there were seen in all sections numerous diffusely disseminated, loosely arranged, glial cells which varied greatly in size and shape. There were numerous multinucleated, immature and poorly differentiated, glial cells.

In some areas, especially in the lower portion of the midbrain there were streams of elongated cells composed predominantly of bipolar spongioblasts. In the midbrain region these cells were so arranged between the partially preserved nerve fibers, that the general structure of the tissue appeared unaltered. The tegmentum of the midbrain was completely spared; the tumor cells being found only within the peduncles.

In sections taken from the left basal ganglia there were a few areas of necrosis and hemorrhage associated with thrombotic occlusion of some of the larger and smaller veins, interspersed in the neoplastic tissue which contained numerous mitotic figures.

In the cortical gray matter of the temporal and occipital lobes there were numerous giant cells diffusely disseminated throughout the otherwise normal tissue. In the occipital lobes there had occurred diffuse infiltration and partial destruction of the optic radiation on both sides.

A small accumulation of tumor cells was found within the left optic tract just posterior to the optic chiasm. A minimum of damage to adjacent nerve fibers had occurred. In the hypothalamus there was a dense neoplastic infiltration confined to the left fornix. The remaining portions of the hypothalamus were normal.

From the standpoint of classification there is little doubt that we are dealing with an unusual type of widespread neoplastic growth with characteristics similar to those described for diffuse cerebral glioblastosis.[1] This was no well circumscribed tumor formation and there had occurred diffuse enlargement of the affected areas with preservation of their general configuration; the absence of demarcation between normal and affected areas and finally the diffuse involvement of large areas of the brain (from the optic chiasm extending to the occipital poles) are all gross features characteristic for diffuse glioblastosis.

The blastomatous proliferation of the glia along certain pathways of the nervous tissue with relative preservation of its normal tissue is one of the striking microscopic changes seen in diffuse glioblastosis. We seem justified in classifying the presented case as a malignant form of diffuse glioblastosis. In cases previously described there were no signs of malignancy and rapid growth. Numerous atypical mitotic figures, giant cells, and areas of necrosis and hemorrhages were found in the case under discussion.

Clinical Diagnosis

Cerebral thromboangiitis obliterans, or
Diffuse neoplastic or demyelinating disease of the posterior cerebrum.

Dr. Evans' Diagnosis

Cerebral thromboangiitis obliterans.

Pathological Diagnosis

Malignant diffuse glioblastosis of the corpus callosum and bilaterally of the occipital and parietal lobes, infiltrating the brain stem via the pyramidal tracts; with foci in the left optic tract, left fornix, and the gray matter of the temporal and occipital lobes.

Dr. Harry M. Salzer: If air studies had been done would they have delineated the process?

Dr. Evans: It is doubtful if this procedure would have been of diagnostic aid.

Dr. Scheinker: The lateral ventricles were quite normal in size; posteriorly the left lateral ventricle was compressed from below.

Student: Does this type of tumor respond to roentgen radiation?

Dr. Evans: One doesn't know; radiation is usually performed with cerebral glioma on the chance of obtaining some improvement.

Student: What is thought about the cramps in the legs?

Dr. Scheinker: The tumor invaded the posterior limb of the left internal capsule and the right parietal white matter. Sensations of pain and tingling may possibly be explained by these localizations of the pathological process; the sensory tracts are closely adjacent to the optic radiation.

REFERENCE

Scheinker, I. M., and Evans, J. P.: "Diffuse Cerebral Glioblastosis," *J. Neuropath. Exp. Neurol.*, 2: 178-189, April 1943.

Diseases of the Nervous System
Index to Volume VII

	Month	Page
ANTISYPHILITIC TREATMENT IN A STATE HOSPITAL, OUTLINE OF *Preston W. Thomas*	February,	55
ARTERIOSCLEROSIS, OBLITERATIVE, OF BRAIN AND KIDNEYS Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	July,	216
BASSOE, PETER — A Tribute *David B. Rotman*	March,	81
BEHAVIOR AS A MEASURE OF OCCUPATIONAL FITNESS *Stephen Weisz*	December,	373
BRAIN FACILITATION NOT BRAIN DESTRUCTION, AIM IN ELECTROSHOCK THERAPY *Paul H. Wilcox*	July,	201
CARE AND TREATMENT OF MENTALLY ILL IN ILLINOIS *Rudolph G. Novick*	May,	139
COMMENT ON "A NEAR FATALITY FROM CURARE" *Matthew Brody*	November,	344
CONTROL OF GRAND MAL EPILEPSY WITH ELECTROSHOCK *John H. Taylor*	September,	284
CONVULSIVE SHOCK THERAPY IN AN ARMY GENERAL HOSPITAL *Mark Zeifert*	April,	112
DILANTIN IN THE TREATMENT OF PSYCHOTIC PATIENTS UNRESPONSIVE TO OTHER TREATMENT *Joseph L. Kubanek and Robert C. Rowell*	*February,*	*47*
DISSEMINATED SCLEROSIS Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	April,	121
ELECTRIC SHOCK THERAPY *James S. L. Jacobs and Warren E. Gilson*	August,	251
ELECTROENCEPHALOGRAPHY IN DIFFERENTIAL DIAGNOSIS OF EPILEPSY AND FAINTING *Frederick C. Redlich*	December,	362
ENCEPHALITIS, TOXOPLASMIC Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	May,	153
EPILEPSY IN THE NAVY *Herman Chor*	February,	37
EQUILIBRIUM NEUROSIS *Ernest Harms*	August,	234
FEAR-ALLAYING EFFECT OF PENTOTHAL SODIUM IN ELECTROSHOCK THERAPY *H. S. Rubinstein*	January,	27
FRIEDREICH'S ATAXIA *H. A. Lipson and J. M. De Nardi*	September,	261
GENESIS OF COMBAT FATIGUE *E. W. Cochran*	July,	211
GLIOBLASTOSIS OF MIDBRAIN AND PONS Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	October,	314
GLIOBLASTOSIS OF PARIETAL AND OCCIPITAL AND OCCIPITAL LOBES Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	December,	376
GROUP PSYCHOTHERAPY IN A CONVALESCENT HOSPITAL *Isidor Bernstein and Herman S. Belmont*	May,	133
GUMMA, FRONTAL LOBES Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	March,	85
HYDROCEPHALUS: Classification and Diagnosis *James Greenwood, Jr.*	July,	209
HYPERTENSIVE BRAIN DISEASE Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	September,	278
INADEQUACIES IN THE LEGAL RECOGNITION AND HANDLING OF THE MENTALLY ILL *Milton H. Erickson*	April,	107
MENINGITIS, TUBERCULOUS Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	January,	23
METABOLISM IN CEREBRAL MALARIA *Mason Trupp*	December,	368
MYASTHENIA GRAVIS *Antonio Austregesilo, Jr.*	April,	116
NEAR FATALITY FROM CURARE PRECEDING ELECTROSHOCK THERAPY *Bruce H. Beard and Titus H. Harris*	September,	276
NEUROLOGICAL COMPLICATIONS OF ESSENTIAL PURPURA HAEMORRHAGICA *Joseph D. Teicher*	June,	170
NEUROPSYCHIATRIC REJECTEES FROM THE STATE OF TENNESSEE (Analysis) *Orman C. Perkins*	January,	9
NEUROSIS — A PROGRESSIVE OR SELF-LIMITING DISEASE *Edmund Bergler*	June,	177
NEUROTIC BEHAVIOR PATTERNS ARISING OUT OF THE COMBAT SITUATION *David B. Vinson, Jr.*	January,	19
NINETY-SIXTH GENERAL HOSPITAL *Henry J. Myers*	October,	310
PARANOIA AND PARANOIAC REACTION TYPES *Harold Rosen and Hugh E. Kiene*	November,	330

	Month	Page
PEDAGOGICAL GROUP PSYCHOTHERAPY *J. W. Klapman*	July,	205
PHYSICIAN'S FIELD WORKERS FOR MENTAL HEALTH *Robert L. Sutherland*	June,	175
PLAN OF ORGANIZATION OF AN INDUSTRIAL HEALTH PROGRAM *V. C. Baird*	September,	273
PREDICTION OF THE IMMEDIATE OUTCOME OF SHOCK THERAPY IN DEMENTIA PRAECOX *Lewis Danziger and Josef A. Kindwall*	October,	299
PREVENTION OF MALADJUSTMENT IN AN ARMY SERVICE FORCES TRAINING CENTER *Eugene Davidoff*	September,	268
PREVENTION OF POSTCONVULSIVE HYPER-EXCITABILITY IN ELECTROSHOCK THERAPY *S. Baumoel*	May,	151
PROBLEMS ENCOUNTERED BY NEUROPSYCHIATRIC SOLDIER PATIENTS ON THEIR FIRST VISIT HOME *Benjamin Simon and Jules D. Holzberg*	July,	197
PROGNOSIS IN SOME MENTAL DISORDERS *Lewis Danziger*	August,	229
PSYCHIATRIC ASPECTS OF HEAD INJURY *A. E. Bennett*	March,	89
PSYCHIATRIC SOCIAL WORK IN THE AMERICAN RED CROSS *Frances Bernhard Weingarten*	March,	75
PSYCHOLOGY OF "BAD INFLUENCE" AND "GOOD ADVICE" *Edmund Bergler*	February,	51
PSYCHONEUROTIC VETERAN *Sidney Rosenbliett and Joseph E. Pisetsky*	June,	165
PSYCHOSOMATIC MEDICINE AND PSYCHIATRY *Burtrum C. Schiele*	April,	101
RECONDITIONING THE NEUROSURGICAL PATIENT *Richard W. Lippman*	November,	325
REFLECTIONS OF AN AMATEUR NEUROPATHOLOGIST *Ben W. Lichtenstein*	August,	244
RELIEF OF SPECIFIC PSYCHIATRIC SYMPTOMS BY CONVULSIVE SHOCK THERAPY *Benjamin Simon and William L. Holt, Jr.*	August,	241
ROLE OF PSYCHIATRY IN INDUSTRY *Lydia G. Giberson*	October,	304
STANDARD TREATMENT OF EPILEPSY *Jerry C. Price and John L. Otto*	November,	345
STATE PROGRAM OF ELEEMOSYNARY CARE *Paul L. Boynton*	January,	5
SUBDURAL HEMATOMA Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	August,	247
SUBDURAL HEMATOMA Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	February,	59
SUB-SHOCK INSULIN THERAPY IN ANXIETY STATES AND ANXIETY DEPRESSIONS *Leslie B. Hohman and Carl L. Kline*	October,	293
SYPHILITIC AMYOTROPHY *Antonio Gonzalez Revilla*	March,	69
THEMATIC APPERCEPTION TEST *Herbert Freed and William F. Eccker*	May,	146
THEORETICAL CONSIDERATIONS OF DEMENTIA PRAECOX *Lewis Danziger*	December,	357
TWO IMPORTANT POST-WAR PROBLEMS IN NEUROLOGICAL SURGERY *Ernest Sachs*	July,	211
VASOPARALYSIS, VASOTHROMBOSIS: (FUNCTIONAL VASCULAR DISTURBANCE OF SMALL CEREBRAL VESSELS) Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	June,	181
VASOTHROMBOSIS WITH SOFTENING, MIDBRAIN, AND SUPERIOR PORTION OF CEREBELLAR HEMISPHERES Neurological Clinical Pathological Conference—*Charles D. Aring*, Editor	November,	338

TWIN ELMS

A Modern Psychiatric Unit

Selected drug and alcohol problems welcome.

Rates moderate.

EUGENE N. BOUDREAU, M.D., *Psychiatrist*
R. STUART DYER, M.D., *Assistant Psychiatrist*

SYRACUSE, N. Y.